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Art Unit	1647
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ENCLOSURES *(Check all that apply)*

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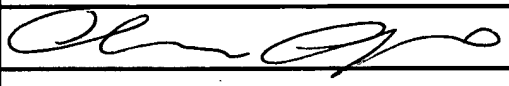
Signature			
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PATENT
Attorney Docket No.: 018512-000410US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

SILVIA and YU

Application No.: 09/623,304

Filed: February 21, 2001

For: IDENTIFICATION AND EXPRESSION OF HUMAN KIR5.1

Customer No.: 20350

Confirmation No. 3840

Examiner: Bridget E. Bunner

Technology Center/Art Unit: 1647

APPELLANT'S REPLY BRIEF UNDER 37 C.F.R. 1.193(b)(1)

Mail Stop Appeal Brief - Patents
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Sir:

This brief is filed in triplicate pursuant to 37 C.F.R. §1.193(b)(1), in response to the Examiner's Answer ("the Answer"), mailed February 24, 2005. A request for an oral hearing pursuant to 37 C.F.R. §1.194 will not be submitted.

I. Utility Rejection and Utility-Based Enablement Rejection

The present invention relates to a novel subunit of an inward rectifier potassium channel, which is termed Kir5.1 and expressed in a variety of tissue and cell types. The instant application asserts a specific and substantial utility of the invention: the identification of human Kir5.1 ion channel subunits allows the identification of modulators of inward rectifier potassium channels comprising the Kir5.1 subunit, which modulators are useful for treating disorders related to abnormal cell excitability in tissues where Kir5.1 is expressed, such as hypertension, acute renal failure, diabetes, *etc.* (*see, e.g.*, page 6, lines 26-31, of the specification). The Examiner has taken the position that the asserted utility is, although credible, not specific or substantial. Appellant will address the specific issues raised in the Answer.

The Asserted Function of Human Kir5.1 Is Valid

On pages 4 and 5 in the Answer, the Examiner expresses doubts about the asserted function of human Kir5.1 as a subunit of an inward rectifier potassium channel. Several references (*e.g.*, Skolnick, Bork, Doerks, Smith, and Brenner) are cited to support the notion that functional assignment solely based on sequence homology is unreliable. Appellant does not agree with the Examiner's reasoning in these arguments.

First, the asserted function of human Kir5.1 as a subunit of an inward rectifier potassium channel is not solely based on its sequence homology to other known inward rectifier channel proteins. The present application has already provided experimental evidence confirming that human Kir5.1 indeed can be a part of an inward rectifier potassium channel (*see, e.g.*, Example II on page 57 of the specification).

Second, the Examiner has on several occasions accepted the asserted role of human Kir5.1 as a subunit of a inward rectifier potassium channel. For instance, in the first full paragraph on page 15 of the Answer, it is stated, "[t]he Examiner acknowledges that based upon the results disclosed in Figure 1 (Example II) of the specification, one

skilled in the art would reasonably recognize the instant Kir5.1 polypeptide as a potassium channel subunit protein." At the bottom of page 18 of the Answer, the Examiner again states, "based on the sequence similarity of the novel nucleic acid molecules of the instant invention to known sequences of inward rectifying potassium channels and the current modulation of Kir5.1 disclosed in Example II of the specification, it can be concluded that the instant Kir5.1 channel could be a novel inward rectifying potassium channel subunit protein." Given these statements, it is puzzling why the Examiner is now questioning the validity of the asserted role of human Kir5.1 as a subunit of an inward rectifier potassium channel.

Third, even if the Examiner had never acknowledged the role of human Kir5.1 as an inward rectifier potassium channel subunit, Appellant contends that under certain circumstances, functional assignment of a newly identified protein based on amino acid sequence homology can be valid and is accepted by those of skill in the art. The cited references provide some general discussions about the pitfalls in sequence-based prediction of protein function, which tend to occur in a situation where functional prediction of a previously unknown protein is made based solely on the presence of a domain with sequence homology to a known functional domain. Appellant does not dispute the general truth stated in these references. The instant case, however, presents a very different situation, where the subject matter of the pending claims is a member of a potassium channel family with well-studied and defined structural features (*e.g.*, transmembrane domains and inward rectifier motif). Most importantly, the experimental results presented in the application have confirmed the role of human Kir5.1 as a subunit of an inward rectifier potassium channel.

The Examiner also cites the papers by Tanemoto *et al.* and Pessia *et al.* to support her position that the asserted role of human Kir5.1 is doubtful. These references, however, do not contradict the role of human Kir5.1 as asserted in this application. For instance, the complete sentence the Examiner has quoted from Tanemoto *et al.* (first paragraph on page 587) states, "Kir5.1 does not belong to any of these subfamilies

(referring to the four previously reproted subfamilies) and its physiological roles are unknown (Bond *et al.*, 1994), though with Kir4.1 it may form a functional K^+ channel in *Xenopus* oocytes (Pessia *et al.*, 1996)." Thus, this sentence merely states that Kir5.1 does not belong to any of the subfamilies previously described in the art, and that it does form a functional potassium channel with Kir4.1, which is consistent with the asserted role of human Kir5.1 as well as the experimental data presented in this application. In addition, Pessia *et al.* clearly state that Kir4.1-Kir5.1 heteromeric channels exist *in vivo* in renal tubular cells and have an apparent role in pH-dependent regulation of K^+ fluxes and acid-based homeostasis (see the second paragraph on page 359 and the last two paragraphs on page 366 of Pessia *et al.*).

As such, Appellant contends that the Examiner has provided no good reason to continue questioning the validity of the asserted role of human Kir5.1 as a subunit of an inward rectifier potassium channel.

The Present Invention Is Not Analogous to Brenner

In the Answer, the Examiner states that because the claimed human Kir5.1 is an "orphan protein," the present case is analogous to *Brenner v. Manson*, 148 USPQ 689 (Sup. Ct. 1966), and that a holding of lack of utility required by 35 U.S.C. §101 is thus appropriate. According to the Examiner, the claimed nucleic acid of the present invention encodes a polypeptide with undetermined functions or biological significance but structural similarity to a family of inward rectifier potassium channels, which is analogous to the *Brenner* case, where a novel compound was asserted to be useful as an anti-tumor agent based on its structural similarity to certain known anti-tumor agents.

Appellant disagrees. The pending claims of the present application are drawn to a nucleic acid encoding an inward rectifier potassium channel subunit, which has been fully characterized both structurally and functionally. Thus, the claimed subject matter has direct utility: it encodes for a polypeptide useful for identifying modulators of

the Kir5.1 channels, which in turn can be used for treating specific diseases (hypertension, acute renal failure, diabetes, *etc.*) In contrast, the *Brenner* case presents a very different situation. The claims in question in *Brenner* are directed to a process of making a steroid, which has unknown activity and is only structurally similar to a compound with tumor-inhibiting effects. The claimed process in *Brenner* therefore has no direct, patentable utility, and the present invention cannot be properly analogized to the one in *Brenner*. Appellant submits that the present case and *Brenner* are factually dissimilar and the Court's holding of insufficient utility in *Brenner* cannot be applied mechanically to the present application.

The Asserted Utility Is Specific

The Examiner takes the position that the asserted utility of the present invention is not specific, because "[s]uch assays can be performed with any polynucleotide or polypeptide" using the general screening method, and that the specification does not disclose any specific "agonists, antagonists, and other modulators that can be identified by this method" (page 10, lines 1-5, of the Answer). Appellant respectfully disagrees. The pending claims are directed to a nucleic acid encoding a specific inward rectifier potassium channel subunit with fully characterized structure and function, which relates to specified disorders (hypertension, acute renal failure, diabetes, *etc.*). The utility of the present invention does not reside in a general screening method, which, according to the Examiner, can be performed with any polypeptide; quite to the contrary, the utility of this invention resides in a specific screening method that can be performed only with the specific type of inward rectifier potassium channels encoded by the claimed nucleic acids, *i.e.*, with the defined structural and functional features, in order to identify modulators of the particular type of potassium channels. This use is therefore specific.

As far as the identity of the specific modulators is concerned, Appellant contends that there should be no requirement for describing the modulators. This is

because the pending claims are directed to a screening method, not to the modulators that can be identified by using the method.

The Examiner further points out that because "a significant number of cation channels" are involved in regulating cell excitability, the asserted utility is therefore not specific (first full paragraph on page 17 of the Answer). Appellant contends that the Examiner's conclusion is erroneously based on an irrelevant truth. The pending claims are directed to a nucleic acid encoding a Kir5.1 channel subunit, which is useful for identification of modulators of a Kir inward rectifier potassium channel. As asserted in the present application, the modulators so identified can be used for treating a number of specified conditions and disorders. The fact that multiple functionally diverse ion channels are present in the tissue and cell types where Kir5.1 is expressed and that the Kir5.1 channels are not unique in regulating cell excitability does not prove the link impossible or even unlikely between the Kir5.1 channels and specific diseases such as hypertension, renal failure, and diabetes.

Furthermore, the Examiner's statement appears to indicate her belief that in order for the modulators of an ion channel to have a specific utility, this ion channel (but not other ion channels) must have a unique role in regulating a physiological process. Appellant cannot agree with the Examiner. One simple example can illustrate the flaw in the Examiner's reasoning. It is well known that ion channel modulators are used for treating hypertension, which would clearly be regarded as a specific utility. Yet, such ion channel modulators often act on multiple ion channels that may be related to hypertension to alleviate the symptoms of the condition. Thus, the Examiner's reference to the involvement of multiple cation channels in regulating cell excitability does not support a reasonable conclusion that the asserted utility is not specific.

The Asserted Utility Is Substantial

The Examiner also takes the position that the asserted utility of the claimed Kir5.1 nucleic acid is not substantial because the present invention is "not complete as filed" and therefore cannot be used "in currently available form" (first full paragraph on page 10 of the Answer). Appellant respectfully disagrees.

The specification teaches assays that can be used for testing candidate compounds for their ability to modulate a Kir5.1 channel activity (*see, e.g.*, pages 40-42 of the specification). Other suitable methods and necessary techniques are also known in the art. Thus, once the polynucleotide and amino acid sequences of a Kir5.1 subunit are disclosed, one of skill in the art can readily use a Kir5.1 channel in such an assay system to screen for and identity modulators of the potassium channel. The claimed invention is therefore useful in its "currently available form." As treating conditions such as hypertension, renal failure, or diabetes is a practical "real-world use," the asserted utility is substantial.

No Objective Reasons for Concluding the Asserted Utility Not Credible

Although the Examiner does not argue that the asserted utility lacks credibility, Appellant is convinced that the utility rejection is at least in part based on the Examiner's disbelief of the asserted utility in the specification. This is evidenced by a number of statement in the Office Actions as well as in the Answer. For instance, on page 9 of the Answer, the Examiner attempts to illustrate why the present invention does not meet the utility requirement. Using one example where a hypothetical specification provides evidence of altered ion channel activity connected to pain perception, the Examiner compares the present application by stating that the application "fails to provide any evidence that this specific Kir5.1 subunit is associated with any particular disease, condition, physiological process other than a general regulation of cell excitability." This statement is made in spite of the specific diseases and conditions

named in the specification, *e.g.*, on page 6, lines 26-31. It is therefore apparent that the Examiner does not believe the utility statement of this application.

As already discussed in the Appeal Brief, MPEP §2107.02 III A indicates that an assertion of utility creates a presumption of utility sufficient for the patentability requirement under 35 U.S.C. §101. To overcome this presumption, it is insufficient to merely question the asserted operability-- the Examiner must carry the initial burden to make a *prima facie* showing of lack of utility by setting forth factual reasons why one of skill in the art would not believe the asserted operability. *In re Gauber*, 187 USPQ 664, 666 (CCPA 1975).

No factual reasons have been offered in the previous Office Actions to support the Examiner's disbelief of the asserted utility. In the Answer, the Examiner cites for the first time the references by Tanemoto *et al.* and Pessia *et al.* to challenge the merits of the asserted utility (*see, e.g.*, pages 5-6 of the Answer). Yet, a close review of the two references indicates that the authors merely provide description of some of the unusual functional features of Kir5.1, such as not belonging to a known subfamily within the inward rectifier potassium channel family or its capability of forming heteromeric channels. These properties, however unusual, do not by any means contradict the utility asserted by the instant specification, that is a modulator of an inward rectifier potassium channel comprising a Kir5.1 subunit can be used for treating a number of specified conditions. Thus, the cited references are not directly relevant to the credibility of the asserted utility. The Examiner has therefore not provided any valid factual basis for holding the asserted utility not credible.

The Claimed Invention Does Provide "Immediate Benefit to the Public"

Appellant in addition wishes to traverse the Examiner's opinion on the present case in connection with the discussion about *Nelson v. Bowler*, 206 USPQ 881 (CCPA 1980). On pages 19-20 of the Answer, the Examiner states, "[i]n the instant case,

assertions that '[b]ecause abnormal ion influx can interfere with the normal physical functions of organ and tissues, compounds capable of modulating ion channels, such as Kir5.1 channels, are useful as therapeutic agents for treating these conditions' (the top of page 16 of the Brief) clearly establish that the instant invention cannot be used 'in a manner which provides some immediate benefit to the public.'" The paragraph quoted from the Appeal Brief simply does not support the Examiner's conclusion of no "immediate benefit," as therapeutic agents for treating diseases and disorders caused by abnormal ion influx and altered cell excitability are most certainly capable of providing "immediate benefit to the public." Therefore, the screening assays useful for identifying these therapeutic agents, *i.e.*, assays utilizing a Kir5.1 polypeptide encoded by the claimed nucleic acid, are also capable of providing "immediate benefit to the public."

The Utility Standard Does Not Require Illustration of Causation of a Disease

Finally, Appellant takes the opportunity to reiterate that the Examiner has improperly imposed an elevated utility standard that requires a direct causal connection to be established between a newly identified protein and specific diseases. This heightened utility standard is inconsistent with the prevailing case law, where the illustration of mechanism is never a part of the utility requirement. This heightened standard is also contrary to sound public policy, which encourages early disclosure of useful new inventions. If, before patent protection can be granted, a patent applicant is required to establish the exact mechanism how a newly identified protein exerts its physiological function despite fully effective uses of this protein, the disclosure of many exciting new discoveries will be greatly delayed.

In summary, Appellant submits that the utility rejection is improper because an improper standard has been applied to assess the utility of the present invention. The withdrawal of the utility rejection is therefore respectfully requested.

Consequently, the enablement rejection based on lack of utility is also improper and should be withdrawn as well.

II. Indefiniteness Rejection

The Examiner has rejected the pending claims for the recitation of hybridization conditions. Despite the arguments and supporting evidence submitted by Appellant, the Examiner continues to argue that because the term "comprising" is used in the claims, hybridization stringency could be lowered before the end of hybridization and therefore allows the claim scope to encompass polynucleotide sequences with relatively low similarity to human Kir5.1.

Appellant respectfully disagrees with the Examiner's reasoning. First and foremost, the claim language expressly requires the claimed nucleic acid to "selectively hybridize[s] under highly stringent hybridization conditions" to a reference polynucleotide sequence, SEQ ID NO:2. Any nucleic acid that can only hybridize to SEQ ID NO:2 under less stringent conditions, which the Examiner considers possible under the term "comprising," simply cannot meet this express requirement and will therefore be excluded from the claim scope.

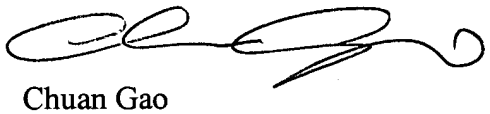
Secondly, even though the open-transitional term "comprising" theoretically allows the inclusion of any additional, unnamed steps in a process, it is inherently necessary, however, that the term allows only the unnamed steps that would not defeat the fundamental purpose of those specifically named steps. Otherwise, there could be no patentable method claims reciting "comprise" or "comprising," as such method claims could always include those unnamed steps undoing what the named steps seek to accomplish.

In the present case, the hybridization conditions are set forth to establish a high stringency condition, which requires a polynucleotide sequence to possess a significant level of sequence homology to SEQ ID NO:2 in order for the polynucleotide

sequence to remain hybridized with SEQ ID NO:2. To allow an additional step of low stringency condition would completely frustrate the purpose of the recited high stringency condition step and render the explicit recitation meaningless. Thus, the Examiner's argument is unreasonable and cannot serve as a logical basis for sustaining the indefiniteness rejection.

In view of the foregoing, Appellant believes all claims now pending in this Application are in condition for allowance.

Respectfully submitted,



Chuan Gao
Reg. No. 54,111

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
CG:cg
60463028 v1